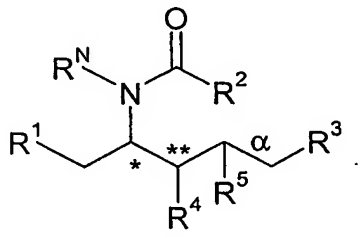
CLAIMS

1. A pharmaceutical formulation comprising:

(i) a drug; and

(ii) a short-chain sphingolipid selected from compounds of the following formula:



wherein:

R^1 is independently:

an O-linked saccharide group; or

an O-linked polyhydric alcohol group;

or:

R^1 is independently:

an O-linked (optionally N-(C_{1-4}alkyl)-substituted amino)-C_{1-6}alkyl-phosphate group; or

an O-linked (polyhydric alcohol-substituted)-C_{1-6}alkyl-phosphate group;

R^2 is independently C_{3-9}alkyl,

and is independently unsubstituted or substituted;

R^3 is independently C_{7-19}alkyl,

and is independently unsubstituted or substituted;

R^4 is independently -H, -OH, or -O-C_{1-4}alkyl;

R^N is independently -H or C_{1-4}alkyl;

the bond marked with an alpha (α) is independently a single bond or a double bond;

if the bond marked with an alpha (α) is a double bond, then R^5 is -H;

if the bond marked with an alpha (α) is a single bond, then R^5 is -H or -OH;

the carbon atom marked (*) is independently in an R-configuration or an S-configuration;

the carbon atom marked (**) is independently in an R-configuration or an S-configuration;

and pharmaceutically acceptable salts, solvates, esters, ethers, chemically protected forms thereof.

* * *

2. A pharmaceutical formulation according to claim 1, wherein said drug is an amphiphilic drug.

3. A pharmaceutical formulation according to claim 1 or 2, wherein said drug is an anthracycline.

4. A pharmaceutical formulation according to claim 1 or 2, wherein said drug is an anti-proliferative anthracycline

5. A pharmaceutical formulation according to claim 1 or 2, wherein said drug is an anti-cancer anthracycline.

6. A pharmaceutical formulation according to claim 1, wherein said drug is selected from: doxorubicin, idarubicin, epirubicin, aclarubicin, mitrozantrone, and daunorubicin, and salts thereof.

7. A pharmaceutical formulation according to claim 1, wherein said drug is doxorubicin or doxorubicin hydrochloride.

8. A pharmaceutical formulation according to claim 1 or 2, wherein said drug is an alkaloid.

9. A pharmaceutical formulation according to claim 1 or 2, wherein said drug is an anti-proliferative alkaloid

10. A pharmaceutical formulation according to claim 1 or 2, wherein said drug is an anti-cancer alkaloid.

11. A pharmaceutical formulation according to claim 1, wherein said drug is selected from: topotecan and camptothecin.

* * *

12. A pharmaceutical formulation according to any one of claims 1 to 11, wherein R^2 is independently linear.

13. A pharmaceutical formulation according to any one of claims 1 to 11, wherein R^2 is independently saturated or partially unsaturated.

14. A pharmaceutical formulation according to any one of claims 1 to 11, wherein R^2 is independently linear; and saturated or partially unsaturated.

15. A pharmaceutical formulation according to any one of claims 1 to 11, wherein R^2 is independently linear; and has from 0 to 3 carbon-carbon double bonds.

16. A pharmaceutical formulation according to any one of claim 1 to 15, wherein R^2 is independently unsubstituted or substituted with from 1 to 3 substituents selected from C_{1-4}alkyl, -OH, C_{1-4}alkoxy, -C(=O)OH, and -C(=O)O-C_{1-4}alkyl.

17. A pharmaceutical formulation according to any one of claims 1 to 11, wherein R^2 is independently $-(CH_2)_nCH_3$, wherein n is an integer from 2 to 8.

18. A pharmaceutical formulation according to any one of claims 1 to 11, wherein R^2 is independently $-(CH_2)_nCH_3$, wherein n is an integer from 4 to 8.

19. A pharmaceutical formulation according to any one of claims 1 to 11, wherein R^2 is independently $-(CH_2)_nCH_3$, wherein n is an integer from 6 to 8.

20. A pharmaceutical formulation according to any one of claims 1 to 11, wherein R^2 is independently $-(CH_2)_6CH_3$.

* * *

21. A pharmaceutical formulation according to any one of claims 1 to 20, wherein the bond marked alpha is independently a double bond and R^5 is -H.

22. A pharmaceutical formulation according to any one of claims 1 to 20, wherein the bond marked alpha is independently a single bond; and R^5 is -H or -OH.

23. A pharmaceutical formulation according to any one of claims 1 to 20, wherein the bond marked alpha is independently $-CH_2-CH_2-$.

24. A pharmaceutical formulation according to any one of claims 1 to 20, wherein the bond marked alpha is independently $-CHOH-CH_2-$.

* * *

25. A pharmaceutical formulation according to any one of claims 1 to 24, wherein R^3 is independently linear.

26. A pharmaceutical formulation according to any one of claims 1 to 24, wherein R^3 is independently saturated or partially unsaturated.

27. A pharmaceutical formulation according to any one of claims 1 to 24, wherein R^3 is independently linear; and saturated or partially unsaturated.

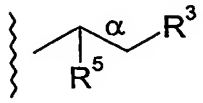
28. A pharmaceutical formulation according to any one of claims 1 to 27, wherein R^3 is independently unsubstituted or substituted with from 1 to 3 substituents selected from C_{1-4}alkyl, -OH, C_{1-4}alkoxy.

29. A pharmaceutical formulation according to any one of claims 1 to 24, wherein R^3 is independently $-(CH_2)_nCH_3$, wherein n is an integer from 8 to 16.

30. A pharmaceutical formulation according to any one of claims 1 to 24, wherein R^3 is independently $-(CH_2)_{12}CH_3$.

* * *

31. A pharmaceutical formulation according to any one of claims 1 to 20, wherein the moiety:



is selected from the following:

$-(CH_2)_8-CH_3$ (from caproic acid) ("C10");
$-(CH_2)_{10}-CH_3$ (from lauric acid) ("C12");
$-(CH_2)_{12}-CH_3$ (from myristic acid) ("C14");
$-(CH_2)_{14}-CH_3$ (from palmitic acid) ("C16");
$-(CH_2)_7-CH=CH-(CH_2)_5-CH_3$ (from palmitoleic acid) ("C16");
$-(CH_2)_{16}-CH_3$ (from stearic acid) ("C18");
$-(CH_2)_7-CH=CH-(CH_2)_7-CH_3$ (from oleic acid) ("C18");
$-(CH_2)_9-CH=CH-(CH_2)_6-CH_3$ (from vaccenic acid) ("C18");
$-(CH_2)_7-[CH=CH-CH_2]_2-(CH_2)_3-CH_3$ (from linoleic acid) ("C18");
$-(CH_2)_7-[CH=CH-CH_2]_3-CH_3$ (from (9,12,15-linoleic acid) ("C18");
$-(CH_2)_4-[CH=CH-CH_2]_3-(CH_2)_3-CH_3$ (from (6,9,12-linoleic acid) ("C18");
$-(CH_2)_7-[CH=CH]_3-(CH_2)_3-CH_3$ (from eleostearic acid) ("C18");
$-(CH_2)_{18}-CH_3$ (from arachidic acid) ("C20");
$-(CH_2)_6-[CH=CH-CH_2]_2-(CH_2)_6-CH_3$ ("C20");
$-(CH_2)_3-[CH=CH-CH_2]_3-(CH_2)_6-CH_3$ ("C20");
$-(CH_2)_3-[CH=CH-CH_2]_4-(CH_2)_3-CH_3$ ("C20");
$-(CH_2)_{20}-CH_3$ (from behenoic acid) ("C22");
analogs wherein the left-most $-(CH_2)_2-$ is replaced with -CH=CH-; and
analogs wherein the left-most $-(CH_2)-$ is replaced with -CH(OH)-.

* * *

32. A pharmaceutical ~~formulation according to~~ any one of claims 1 to 31, wherein R^4 is independently -H, -OH, -OMe, -OEt, -O(iPr), -O(nPr), -O(nBu), -O(iBu), -O(sBu), or -O(tBu).

33. A pharmaceutical formulation according to any one of claims 1 to 31, wherein R^4 is independently -H, -OH, or -OMe.

34. A pharmaceutical formulation according to any one of claims 1 to 31, wherein R^4 is independently -H or -OH.

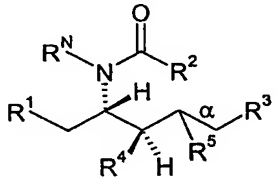
35. A pharmaceutical formulation according to any one of claims 1 to 31, wherein R^4 is independently -OH.

* * *

36. A pharmaceutical formulation according to any one of claims 1 to 35, wherein R^N is independently -H, -Me, or -Et.

* * *

37. A pharmaceutical formulation according to any one of claims 1 to 36, wherein the carbon atoms marked (*) and (**) have a configuration as shown in the following formula:



38. A pharmaceutical formulation according to any one of claims 1 to 36, wherein the carbon atoms marked (*) and (**) have the same configuration as in naturally occurring sphingosine.

* * *

39. A pharmaceutical formulation according to any one of claims 1 to 38, wherein R^1 is independently:

an O-linked saccharide group; or

an O-linked polyhydric alcohol group.

40. A pharmaceutical formulation according to any one of claims 1 to 38, wherein R^1 is independently an O-linked saccharide group.

41. A pharmaceutical formulation according to any one of claims 1 to 38, wherein R^1 is independently an O-linked mono-, di-, or tri-saccharide group.

42. A pharmaceutical formulation according to any one of claims 1 to 38, wherein R^1 is independently an O-linked mono- or di-saccharide group.

43. A pharmaceutical formulation according to any one of claims 1 to 42, wherein R^1 is formed from pentose and/or hexose groups.

44. A pharmaceutical formulation according to any one of claims 1 to 42, wherein R^1 is formed from a group or groups selected from:

arabinose, lyxose, ribose, or xylose;

allose, altrose, glucose, mannose, gulose, idose, galactose, or talose;

and derivatives thereof.

45. A pharmaceutical formulation according to any one of claims 1 to 42, wherein R^1 is independently an O-linked mono-, di-, or tri-saccharide group derived from:

arabinose, lyxose, ribose, or xylose;

allose, altrose, glucose, mannose, gulose, idose, galactose, or talose;

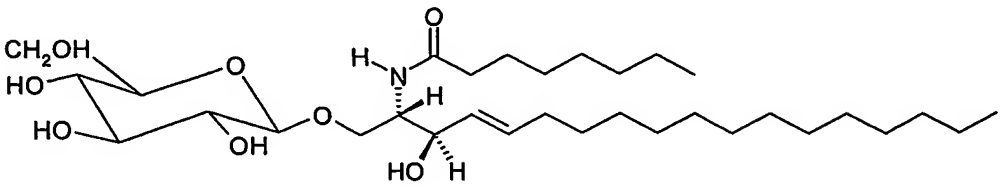
sucrose, maltose, lactose, cellobiose, or galabiose;

globotriaose, isoglobotriaose, mucotriaose, lactotriaose, neolactotriaose gangliotriaose, galatriaose, mollutriaose, or antrotriaose;

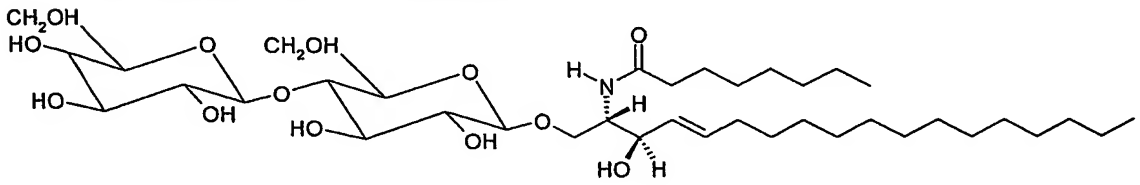
or a derivative thereof.

46. A pharmaceutical formulation according to claim 44 or 45, wherein said saccharide group derivatives are selected from deoxy, di-deoxy, di-deoxy-di-dehydro, methoxy (-OMe), acetoxy (-OC(=O)Me), carboxylic acid (-C(=O)OH), sulfuric acid ($-OSO_3H$), amino-deoxy (e.g., $-NH_2$), N-acetyl-amino-deoxy (e.g., -NHC(=O)Me), or N-sulfo-amino-deoxy (e.g., $-NHS(O)_2OH$) derivatives.

47. A pharmaceutical formulation according to claim 1, wherein said short-chain sphingolipid has the following formula (C_8-GlcCer):



48. A pharmaceutical formulation according to claim 1, wherein said short-chain sphingolipid has the following formula:



49. A pharmaceutical formulation according to any one of claims 1 to 38, wherein R^1 is independently an O-linked polyhydric alcohol group.

50. A pharmaceutical formulation according to claim 49, wherein R^1 is formed from groups selected from: ethanediol (glycol), propanediol, butanediol, glycerol, and erythritol.

* * *

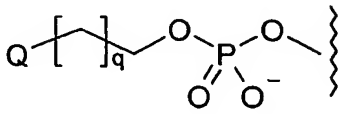
51. A pharmaceutical formulation according to any one of claims 1 to 38, wherein R^1 is independently:

an O-linked (optionally N-(C_{1-4}alkyl)-substituted amino)-C_{1-6}alkyl-phosphate group; or

an O-linked (polyhydric alcohol-substituted)-C_{1-6}alkyl-phosphate group.

52. A pharmaceutical formulation according to any one of claims 1 to 38, wherein R^1 is independently an O-linked (optionally N-(C_{1-4}alkyl)-substituted amino)-C_{1-6}alkyl-phosphate group.

53. A pharmaceutical formulation according to any one of claims 1 to 38, wherein R^1 is independently:



wherein:

q is independently an integer from 0 to 5;

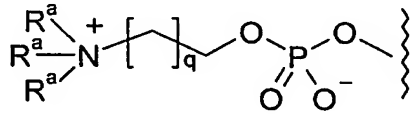
Q is independently: $-NH_2$, $-NHR^a$, $-NR^a{}_2$, or $-NR^a{}_3{}^+$; or:

Q is independently a polyhydric alcohol group, linked via an oxygen atom;

each R^a is independently linear or branched saturated C_{1-4}alkyl.

54. A pharmaceutical formulation according to claim 53, wherein Q is independently: $-NH_2$, $-NHR^a$, $-NR^a{}_2$, or $-NR^a{}_3{}^+$.

55. A pharmaceutical formulation according to any one of claims 1 to 38, wherein R^1 is independently:

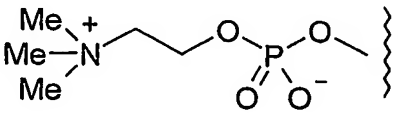


wherein:

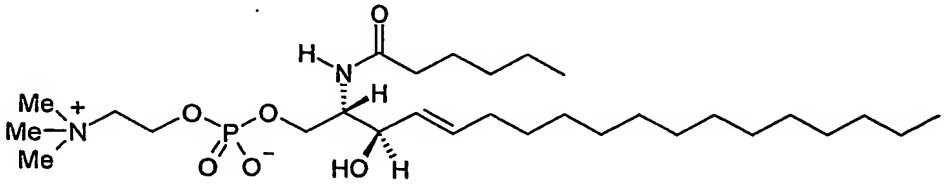
q is independently an integer from 0 to 5; and

each R^a is independently a C_{1-4}alkyl group.

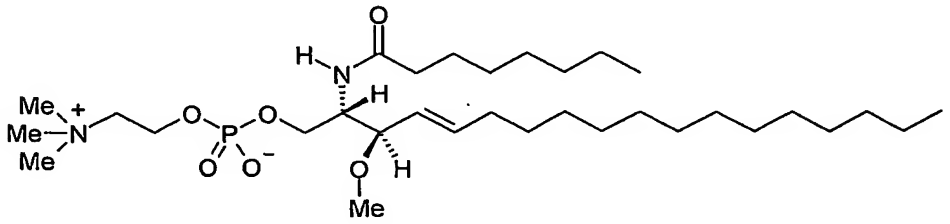
56. A pharmaceutical formulation according to any one of claims 1 to 38, wherein R^1 is independently:



57. A pharmaceutical formulation according to claim 1, wherein said short-chain sphingolipid has the following formula ("C_6-SM"):



58. A pharmaceutical formulation according to claim 1, wherein said short-chain sphingolipid has the following formula ("3-O-methyl-C_6-SM"):



59. A pharmaceutical formulation according to claim 53, wherein Q is independently a polyhydric alcohol group, linked via an oxygen atom.

60. A pharmaceutical formulation according to claim 59, wherein Q is formed from a group selected from: ethanediol (glycol), propanediol, butanediol, glycerol, and erythritol.

* * *

61. A pharmaceutical formulation according to any one of claims 1 to 60, wherein said pharmaceutical formulation additionally comprises one or more other pharmaceutically acceptable ingredients selected from pharmaceutically acceptable carriers, diluents, excipients, adjuvants, fillers, buffers, preservatives, anti-oxidants, lubricants, stabilisers, solubilisers, and surfactants.

62. A pharmaceutical formulation according to any one of claims 1 to 61, wherein said pharmaceutical formulation is suitable for parenteral administration.

* * *

63. A pharmaceutical formulation according to any one of claims 1 to 62, wherein the pharmaceutical formulation is a liposomal pharmaceutical formulation.

* * *

64. A liposomal pharmaceutical formulation according to claim 63, wherein the liposomes of the liposomal pharmaceutical formulation are prepared using a mixture of lipids comprising, at least, vesicle-forming lipids and said short-chain sphingolipid.

65. A liposomal pharmaceutical formulation according to claim 64, wherein said mixture of lipids comprises phospholipids and said short-chain sphingolipid.

66. A liposomal pharmaceutical formulation according to claim 64, wherein said mixture of lipids comprises phospholipids, cholesterol, and said short-chain sphingolipid.

67. A liposomal pharmaceutical formulation according to claim 64, wherein said mixture of lipids comprises phosphatidylcholines, cholesterol, and said short-chain sphingolipid.

68. A liposomal pharmaceutical formulation according to claim 64, wherein said mixture of lipids comprises fully hydrogenated soy phosphatidylcholine (HSPC), cholesterol, and said short-chain sphingolipid.

69. A liposomal pharmaceutical formulation according to claim 64, wherein said mixture of lipids comprises dipalmitoyl-phosphatidylcholine (DPPC), cholesterol, and said short-chain sphingolipid.

70. A liposomal pharmaceutical formulation according to any one of claims 64 to 69, wherein said mixture of lipids additionally comprises a vesicle-forming lipid which is derivatized with a polymer chain.

71. A liposomal pharmaceutical formulation according to any one of claims 64 to 69, wherein said mixture of lipids additionally comprises a phosphatidylethanolamine (PE) which is derivatized with polyethyleneglycol (PEG).

72. A liposomal pharmaceutical formulation according to any one of claims 64 to 69, wherein said mixture of lipids additionally comprises N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG2000-DSPE).

* * *

73. A liposomal pharmaceutical formulation according to any one of claims 64 to 72, wherein the amount of short-chain sphingolipid1-25 mol%.

74. A liposomal pharmaceutical formulation according to any one of claims 64 to 73, wherein the amount of cholesterol, if present, is 20-50 mol%.

75. A liposomal pharmaceutical formulation according to any one of claims 64 to 74, wherein the amount of phospholipid, excluding phospholipid which is derivatized with a polymer chain, if present, is 45-70 mol%.

76. A liposomal pharmaceutical formulation according to any one of claims 64 to 75, wherein the amount of vesicle-forming lipid which is derivatized with a polymer chain, if present, is 1-15 mol%.

77. A liposomal pharmaceutical formulation according to any one of claims 64 to 76, wherein said liposomes of said liposomal pharmaceutical formulation comprise 0.05-0.50 µmol drug per µmol phospholipid.

* * *

78. A liposomal pharmaceutical formulation according to any one of claims 64 to 77, wherein said liposomes additionally comprise other pharmaceutically acceptable ingredients selected from: ammonium sulfate, histidine, hydrochloric acid and/or sodium hydroxide, sucrose, and water-for-injection.

* * *

79. A liposomal pharmaceutical formulation according to any one of claims 64 to 78, wherein said liposomes have a mean diameter of 50 to 150 nm.

* * *

80. Caelyx® or Doxil® liposomes post-inserted with a short-chain sphingolipid as defined in any one of claims 1 and 12 to 60.

* * *

81. A pharmaceutical formulation according to any one of claims 1 to 80, for use in a method of treatment of the human or animal body by therapy.

82. Use of:
(i) a drug, as defined in any one of claims 1 to 11; and
(ii) a short-chain sphingolipid, as defined in any one of claims 1 and 12 to 60;
in the manufacture of a medicament for the treatment of a proliferative condition in a human or animal patient.

83. Use according to claim 82, wherein said proliferative condition is cancer.

84. Use according to claim 82, wherein the drug is doxorubicin or a salt thereof; and the proliferative condition is a proliferative condition that is treated by doxorubicin or a salt thereof.

85. A method of treating a proliferative condition comprising administering to a patient in need of treatment an effective amount of a pharmaceutical formulation according to any one of claims 1 to 80.

86. A method according to claim 85, wherein said proliferative condition is cancer.

87. Use according to claim 85, wherein the drug is doxorubicin or a salt thereof; and the proliferative condition is a proliferative condition that is treated by doxorubicin or a salt thereof.

88. A method of making a pharmaceutical formulation according to any one of claims 1 to 79, comprising the step of admixing said drug and said short-chain sphingolipid.

89. A method of making a liposomal pharmaceutical formulation according to any one of claims 63 to 80, comprising the steps of:

(a) forming a lipid mixture comprising, at least, vesicle-forming lipids and said short-chain sphingolipid;

(b) forming liposomes from said lipid mixture; and

(c) adding said drug to the liposomes formed in (b);

thereby forming liposome-entrapped drug.

90. A method of making a liposomal pharmaceutical formulation according to any one of claims 63 to 79, comprising the steps of:

(a) forming a lipid mixture comprising, at least, vesicle-forming lipids and said short-chain sphingolipid;

(b) adding said drug to said lipid mixture;

(c) forming liposomes from the mixture formed in (b);

thereby forming liposome-entrapped drug.

* * *

91. A method of increasing the bioavailability and/or cellular uptake of a drug, as defined in any one of claims 1 to 11, which method includes the step of co-administering said drug with a short-chain sphingolipid, as defined in any one of claims 1 and 12 to 60.